REMARKS

Claims 1, 17, 22-24, 31, 32, 45-56, 58-65 and 67-69 are pending and claims 2-16, 18-21, 25-30, 33-44, 57, and 66 are canceled.

35 U.S.C. § 103 Rejections

Applicants submit that the rejections under 35 U.S.C. § 103 addressed below are in error for the following reasons.

Legal Framework

Initially, the determination of whether a claim is obvious under 35 U.S.C. § 103 depends on at least four underlying factual issues set forth in *Graham v. John Deere Co. of Kansas City*[1]: (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art; and (4) evaluation of any relevant secondary considerations. In April 2007, the Supreme Court affirmed the *Graham* analysis as the framework for determining obviousness.[2]

In addressing the scope and content of the prior art, references are not pertinent to an obviousness inquiry if they are not from analogous art.[3] A reference is analogous art if: (1) the reference is from the same field of endeavor, regardless of the problem addressed, or (2) the reference is not within the inventor's field of endeavor, yet it is reasonably pertinent to the particular problem addressed by the inventor. In *Clay*, the PTO asserted that the claimed invention and the Sydansk reference were part of a common endeavor of "maximizing withdrawal of petroleum stored in petroleum reservoirs."[4] Sydansk taught the

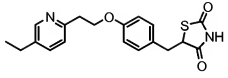
> use of a gel in unconfined and irregular volumes within generally underground natural oil-bearing formation to channel flow in a desired direction; Clay teaches the introduction of gel to the confined dead volume of a man-made storage tank.[5]

[1] 383 U.S. 1, 17, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966).
[2] *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1739 (2007).
[3] *In re Clay*, 23 U.S.P.Q.2d 1058, 1060 (Fed. Cir. 1992).
[4] *Id.*
[5] *Id.*

However, the Federal Circuit disagreed with the Office and held that Clay's field of endeavor was "*storage* of refined liquid hydrocarbons" and Sydansk's invention was directed to the "*extraction* of crude petroleum."

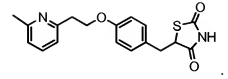
The second step of the *Graham* analysis requires consideration of the differences between the prior art and the claims at issue. It is well established law, that, where, as here, the claims at issue are directed toward a chemical compound, the analysis of the *Graham* factor on the differences between the claimed invention and the prior art often turns on the structural similarities and differences between the claimed compound and the prior art compounds.[6] Obviousness based on structural similarity thus requires identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound.[7]

In *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*,[8] the Federal Circuit addressed the obviousness issue for structurally similar chemical compounds. In *Takeda*, the claim at issue recited pioglitazone (5-{4-[2-(5-ethyl-2-pyridyl)ethoxy] benzyl}-2,4-thiazolidinedione) having the following structure:



An ethyl substituent is attached to the 5-position on the pyridyl ring.

Alphapharm filed an ANDA to manufacture and sell a generic version of pioglitazone. According to Alphapharm, Takeda's claimed compound would have been obvious over the prior art compound TZD ("compound b": a pyridyl ring with a methyl (CH_3) group attached to the 6-position of the ring),[9] having the following structure:



[6] *See Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1377; 81 USPQ2d 1324 (Fed. Cir. 2006).
[7] *See Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356; 83 USPQ2d 1169 (Fed. Cir. 2007).
[8] 492 F.3d 1350 (Fed. Cir. 2007).
[9] *Id.* at 1354.

Alphapharm argued that one of ordinary skill in the art would select compound b for antidiabetic research and then make "two obvious chemical changes: first, homologation, i.e., replacing the methyl group with an ethyl group, which would have resulted in a 6-ethyl compound; and second, 'ring-walking,' or moving the ethyl substituent to another position on the ring, the 5-position, thereby leading to the discovery of pioglitazone."[10]

The district court found, however, that one of ordinary skill in the art would not have selected compound b from the "hundreds of millions" of possible compounds. "[T]he prior art did not suggest to one of ordinary skill in the art that compound b would be the best candidate as the lead compound for antidiabetic research."[11] Moreover, when determining the obviousness of new chemical compounds, there must be "some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness."[12]

Once a reason to modify a known compound is found, the skilled person must also have a reasonable expectation that such a modification will be successful or beneficial in some way. In many chemical cases a "reasonable expectation of success" is not always found, as the Federal Circuit stated in *Eisai Co. v. Dr. Reddy's Laboratories, Inc.*[13] :

> First, KSR assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions. Second, KSR presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound. See Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007). ("Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."). Third, the Supreme Court's analysis in KSR presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions," 127 S. Ct. at 1742. In Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008), this court further explained that this "easily traversed, small and finite number of alternatives . . . might support an inference of obviousness." To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a

[10] *Id.* at 1357.
[11] *Id.* at 1358.
[12] *Id.*
[13] *Eisai Co. v. Dr. Reddy's Laboratories, Inc.*, 87 U.S.P.Q.2d 1452 (Fed. Cir. 2008).

difficult hurdle because potential solutions are less likely to be genuinely predictable. (Emphasis added)

Notenbomer in view of Macek and Bogentoft

In the context of this legal precedent, reconsideration is respectfully requested of the rejection of claims 1, 17, 22-24, 31, 32, 45-56, 58-65, and 67-69 as unpatentable over Notenbomer (EP 0 730 494) in view of Macek et al. (U.S. Patent No. 3, 499,960) and Bogentoft (EP 0 040 590) under 35 U.S.C. § 103(a).

Claim 1

Claim 1 is directed to an oral or rectal pharmaceutical composition comprising a pharmaceutically acceptable excipient and core-shell particles. These core-shell particles comprise a core component and a shell component; the core component comprises a potassium-binding cation exchange polymer and the shell component comprises a crosslinked polymer produced by free radical polymerization of an ethylenic monomer selected from the group consisting of acrylic, methacrylic, styrenic, dienic, vinylic and combinations thereof. The shell component is essentially not disintegrated during residence and passage through the gastro-intestinal tract of an animal subject.

Notenbomer generally discloses methods and particles for binding monovalent cations. The particles have a nucleus and a coating; the nucleus contains a cation exchange material and the coating comprises a membrane that is permeable for monovalent cations. This coating is disclosed as being more permeable for monovalent cations than for bi- or higher valent cations. Exemplified cation exchange materials are polyphosphate and polystyrene sulfonate resins. Exemplified coatings are cellulose acetate and crosslinked polyethyleneimine. Generally, these particles are disclosed for treating hypertension. The polyethyleneimine shells of Notenbomer do not contain repeat units derived from an acrylic, methacrylic, styrenic, dienic, or vinylic monomer because they are prepared by ring opening polymerization of ethylene imine having the following structure.

Ethylene imine is not an acrylic (H_2C=C(R)-C(O)-R), methacrylic (H_2C=C(CH_3)-C(O)-R), styrenic (C_6H_5-C(R)=CH_2), dienic (CH_2=C(R)-R-C(R)=CH_2), or vinylic (R-C(R)=CH_2) monomer[14] because it does not contain a double bond as required for all the members of the Markush group. Further, the polyethyleneimine shell of Notenbomer contains a nitrogen atom in the backbone of the polymer whereas the polymer shell of claim 1 contains only carbon atoms in the backbone of the polymer.

The Office states that while Notenbomer is "silent to the specific coating materials of the instant claims. The coating of ionic exchange resins with crosslinked polymers is well known in the art ...."[15] The Office further states that it would have been obvious "to coat the ionic exchange resins of the '494 patent with the polymers of the '960 patent since both patents solve the problem of binding ions in the gastrointestinal tract."[16]

Macek et al. disclose polymers used to remove bile acids; the polymers disclosed are polystyrene resins crosslinked with divinyl benzene and functionalized through chloromethylation of the aromatic rings and replacement of the chlorine atom with a tertiary amine such as trimethyl amine to form a trimethyl ammonium group attached to the aromatic rings. Thus, the polymers are amine polymers that can be coated with carboxypolymethylene crosslinked with polyallyl sucrose or an acrylic acid polymer crosslinked with polyallylsucrose. Further, Macek is directed to bile acid binders that have a core of an amine polymer and a shell that can be an acrylic acid polymer and provides a palatable composition. An amine polymer core binds anions (e.g., bile acids) and would <u>not</u> be a potassium binding cation exchange polymer as required by the instant claims.

Bogentoft (the '590 patent) discloses an oral pharmaceutical preparation comprising a core containing a therapeutically active substance and a coating. The core can include typical pharmaceutically inactive materials like polysaccharides, microcrystalline cellulose, starch, and waxes.[17] The coating comprises an anionic carboxylic acrylic polymer soluble only above pH 5.5 in an amount of 10 to 85 wt.% of the coating and a water-insoluble polymer selected from

[14] Note that R in these monomers can independently be various substituents as known in the art. The formulae are presented to support the difference in the monomer structures as compared to ethylene imine.
[15] See Office action dated September 28, 2009 at page 3.
[16] See *id.* at page 4.
[17] EP 0040590, page 4, lines 27-29

quaternary ammonium substituted acrylic polymers in an amount of 15-90 wt.% of the coating. The coating normally has a thickness of 3-60 um, preferably 10-30 um.[18]

In *Clay*, the PTO asserted that the claimed invention and the Sydansk reference were of a common endeavor because they were directed to "maximizing withdrawal of petroleum stored in petroleum reservoirs."[19] Similarly, the Office asserts that "it would have been obvious to apply the acrylic polymer to the ionic exchange resin of the combination in order to provide an even and stable formulation that allowed ions to pass through."[20] While the Office states that the Macek patent and the Notenbomer patent can be combined to provide an "even and stable formulation," this reason does not place Applicants' invention in the same field as the Macek patent nor does it address the problem disclosed in either Applicants' specification or the Notenbomer patent.

For example, there are many differences between binding sodium and potassium even though they are similar target ions. These differences include variances in the relative and absolute amounts of sodium and potassium along the gastrointestinal tract; the amounts of sodium and potassium depending upon the condition suffered by the patient; and the selectivity of a cation exchange polymer for sodium and potassium ions.

The amount of sodium as compared to the amount of potassium available for binding will be different because the relative and absolute amounts of sodium and potassium in the gastrointestinal tract change depending on location (e.g., distance from the stomach). For example, Fordtran et al.,[21] who studied the sodium and potassium concentrations in the upper GI after different meals, (see especially Figs 2, 4 and 10), found that at the end of the ileum, the sodium concentration is relatively high, whereas the potassium concentration is relatively low. However, at the end of the gastrointestinal tract, the contents have a relatively high potassium concentration and a relatively low sodium concentration.[22]

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[18] EP 0040590, page 3, lines 11-20.

[19] *Clay*, 23 U.S.P.Q.2d at 1060.

[20] See Office action dated September 28, 2009 at page 4.

[21] J.S. Fordtran et al. "Ionic Constituents and Osmolality of Gastric and Small-Intestinal Fluids after Eating," *Am. J. Digestive Dis.* **1966**, *11(7)*, 503.

[22] O. Wrong et al., "*In Vivo* Dialysis of Faeces as a Method of Stool Analysis," *Clin. Sci.* **1965**, *28*, 357-375. (see Figures 2 and 4).

Further, when a subject suffers from hyperkalemia, the body compensates for the high intracellular potassium concentration in various ways, and thus, the amount of sodium or potassium found within the gastrointestinal tract in a hyperkalemic patient can be much different from the sodium and potassium concentrations of healthy people or patients suffering from various diseases. For example, clinical evidence shows that hyperkalemic patients with renal dysfunction or chronic kidney disease (CKD) who are not on dialysis increase potassium excretion in the terminal colon, as described in the review by Musso.[23] Specifically, Musso states:

> During CKD, the small intestine makes a greater contribution to potassium excretion than it does under normal conditions. Intestinal potassium excretion rises during chronic renal failure and the body can eliminate an additional 10–20 mmol of potassium by this route. Colonic potassium secretion begins to adapt when glomerular filtration is reduced to around one-third of normal and when renal failure is advanced, this route may account for as much as 30–70% of total potassium excretion.

This means that depending on the patient, the same cation-binding polymer can have a different effect on potassium and sodium concentrations in the body. Patients on drugs that affect potassium secretion, such as potassium sparing and non-potassium sparing diuretics, will have various perturbations in their sodium/potassium balance that may affect potassium and sodium availability in the gastrointestinal tract. Thus, these patients could also experience a different effect on potassium and sodium concentrations in the body upon administration of a cation-binding polymer.

As *KSR v. Teleflex* and *Takeda v. Alphapharm* emphasize, it is important to "identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does."[24] Although the Office states that providing an even and stable coating would be the reason for combining the references, similar to *Ex parte Meagher*, such a general statement for the reason for combining the references does not indicate why one would select the Macek or Bogentoft patents from the multitude of

[23] C.G. Musso, "Potassium Metabolism in Patients with Chronic Kidney Disease (CKD), Part I: Patients Not on Dialysis (Stages 3-4)," *International Urology and Nephrology* **2004**, *36*, 465-468.

[24] *KSR v. Teleflex, Inc.*, 82 U.S.P.Q.2d 1385, 1396.

references describing the possible coatings.[25] Further, there is no reason provided in the cited art or reliance on knowledge in the art that would have led a skilled person to select Bogentoft from the universe of coatings for pharmaceutical compositions. Bogentoft does not disclose a potassium-binding or cation exchange core polymer, but describes a core of an active agent and common pharmaceutical excipients. Further, the coating described by Bogentoft is soluble above pH 5.5 and thus disintegrates in the colon to release the active agent. Thus, the coating does not meet the requirement of claim 1 that the shell polymer be "essentially not disintegrated during residence and passage through the gastro-intestinal tract of an animal subject." Thus, there is no reason to combine the Bogentoft reference with the Notenbomer and Macek references.

Even if the PTO is relying on the Macek and Bogentoft references as non-analogous art recited to show the common knowledge of one of ordinary skill in the art, the Office has not articulated a reason why a skilled person would have selected the claimed shell polymers to combine with the potassium-binding polymers. Also, neither Macek nor Bogentoft evidence common general knowledge of a person of ordinary skill in the art that would have provided a reason to combine the cited patents.

Further, even if there were a reason to combine the Notenbomer, Macek, and Bogentoft references for any purpose, there would not have been a reasonable expectation of success that the coated particles would be beneficial for potassium binding. For example, the core of the Macek particle is a polystyrene polymer with pendant ammonium groups and the core of the Bogentoft particle is an active agent mixed with a pharmaceutical excipient. Neither of these core compositions is similar to the potassium-binding polymer required by claim 1. Thus, it would be unpredictable whether an even and stable formulation could be formed with a significantly different core material than those described by Macek or Bogentoft.

Thus, claim 1 and the claims that depend therefrom are patentable in view of the cited references.

[25] *Ex parte Meagher*, Appeal no. 2008-3613; Application No. 10/380,898 decided September 22, 2008 at page 15 (describing that combining references for the purpose of "obtaining a conversion coating having good corrosion resistance and good top coat adhesion properties-which are likely goals of virtually every conversion coating composition-do not provide the ordinary coating formulations chemist with a reason to systematically vary" the prior art compositions to arrive at the claimed composition.).

Claim 45

Claim 45 is directed to a method of removing potassium ion from a gastrointestinal tract of an animal subject suffering from renal insufficiency or renal failure. The method comprises administering core-shell particles comprising a core component and a shell component, the core component comprising a potassium-binding cation exchange polymer and the shell component comprising a polymer being produced by free radical polymerization of an ethylenic monomer; binding potassium ion with the core-shell particles in the gastrointestinal tract of the animal subject; and retaining bound potassium ion with the core-shell particles during residence and passage of the core-shell particles through the gastro-intestinal tract of the animal subject, such that potassium ion is removed from the gastrointestinal tract of the animal subject by the core-shell particles to obtain a therapeutic and/or prophylactic benefit.

The Office states that it would have been obvious to treat hyperkalemia with the combined prior art.[26] The Office further asserts that the "combined prior art comprises the ion exchange resin of the '494 patent coated by the coating of the '960 patent."[27] Also, the Office asserts that the Macek particles are "used for binding bile in the GI tract, bile comprising potassium ions, and would have been an obvious addition to a potassium binding particle."[28] However, the definition of bile follows.

> The yellowish brown or green fluid secreted by the liver and discharged into the duodenum where it aids in the emulsification of fats, increases peristalsis, and retards putrefaction; contains sodium glycocholate and sodium taurocholate, cholesterol, biliverdin and bilirubin, mucus, fat, lecithin, and cells and cellular debris.[29]

It is noted that bile does not contain potassium ions, but does contain sodium glycocholate and sodium taurocholate. Further, Macek et al. state that polymers that are effective for removing bile acids *in vivo* can bind glycocholic acid in an aqueous solution.[30] Thus, contrary to the Offices assertion, bile does not contain potassium ions and the Macek particles would not have bound positive ions such as potassium.

[26] See Office action dated September 28, 2009 at page 4.
[27] See Office action dated September 28, 2009 at page 4.
[28] See Office action dated September 28, 2009 at page 4.
[29] Stedman's Medical Dictionary, 26th Ed., 1995.
[30] See U.S. Patent No. 3, 499,960 at column 1, lines 56-61.

Further, none of the references discloses the population of patients that suffer from renal insufficiency or renal failure. Notenbomer discloses methods for treating hypertension, Macek discloses various bile acid binders for hypercholesteremia and biliary cirrhosis, and Bogentoft discloses active agent formulations for treating hypercholesteremia (colestyramine), ulcerative colitis and rheumatoid arthritis (salicylazosulfapyridine) and inflammation (5-aminosalicylic acid). Thus, the element of a patient suffering from renal insufficiency or renal failure is missing from the combination of the references. Thus, claim 45 and the claims that depend therefrom are patentable over the cited references.

In sum, claims 1, 17, 22-24, 31, 32, 46-50, 54-63, and 67-69 are patentable over Notenbomer (EP 0 730 494) in view of Cohen et al. (U.S. Patent No. 6,558,665) under 35 U.S.C. § 103(a).

CONCLUSION

Applicant submits that the present application is now in condition for allowance and requests early allowance of the pending claims.

The Commissioner is hereby authorized to charge any under payment or credit any over payment to Deposit Account No. 19-1345.

Respectfully submitted,

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